

## Re-examining Permissive Hypercapnia in ARDS

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# Accepted Manuscript

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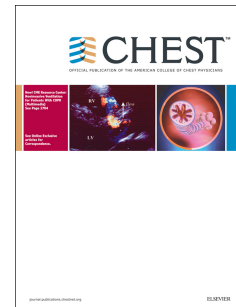
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## **Re-examining permissive hypercapnia in ARDS: A narrative review**

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## Abbreviations

Abbreviation	Definition
ABG	Arterial Blood Gas
ACP	Acute Cor Pulmonale
ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Interval
CO <sub>2</sub>	Carbon Dioxide
CVP	Central Venous Pressure
Ees:Ea	Ratio of elastance of right ventricle to elastance of pulmonary artery system
ECLS	Extra Corporeal Life Support
HA	Hypercapnic Acidosis
HR	Heart Rate
IL-8	Interleukin 8
LPV	Lung Protective Ventilation
mPAP	Mean Pulmonary Arterial Pressure
MV	Mechanical Ventilation
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OR	Odds Ratio
PA	Pulmonary Artery
PaCO <sub>2</sub>	Partial Pressure of arterial Carbon Dioxide
PaO <sub>2</sub>	Partial Pressure of arterial Oxygen
PBW	Predicted Body Weight
PEEP	Positive End Expiratory Pressure
Ppao	Pulmonary artery Occlusion Pressure
Pplat	Plateau Pressure
PVR	Pulmonary Vascular Resistance
RV	Right Ventricle
RVEDA/LVEDA	Ratio of Right Ventricular End Diastolic Area to Left Ventricular End Diastolic Area
RVEF	Right Ventricular Ejection Fraction
RVSWI	Right Ventricular Stroke Work Index
SVR	Systemic Vascular Resistance
TEE	Trans Esophageal Echocardiography
TTE	Trans Thoracic Echocardiography
VILI	Ventilator Induced Lung Injury

**Abstract**

Lung protective ventilation has become the cornerstone of management in patients with ARDS. A subset of patients are unable to tolerate lung protective ventilation without significant carbon dioxide elevation. In these patients permissive hypercapnia is used. Although thought to be benign, it is becoming increasingly evident that elevated carbon dioxide levels have significant physiological effects. In this narrative review, we highlight clinically relevant end organ effects in both animal models and clinical studies. We also explore the association between elevated carbon dioxide, acute cor pulmonale and ICU mortality. We conclude with a brief review of alternative therapies for CO<sub>2</sub> management currently under investigation in patients with moderate to severe ARDS.

**Keywords:**

Permissive hypercapnia

Mechanical Ventilation

Acute respiratory distress syndrome

Acute cor pulmonale

Right ventricular dysfunction

## 1. Introduction

An improved understanding of the pathophysiology and clinical management of acute respiratory distress syndrome (ARDS) has led to lung protective ventilation (LPV) becoming a cornerstone of management. Early strategies of mechanical ventilation in ARDS were tailored to achieve tidal volume ventilation of 10-15 ml/kg predicted body weight (PBW) <sup>1</sup>. High pressure, high tidal volume ventilation strategies were utilized to overcome densely consolidated, poorly compliant lung regions in an effort to achieve adequate arterial oxygenation and normal carbon dioxide (CO<sub>2</sub>) levels <sup>2,3</sup>. This notion was disproven when the landmark ARMA trial by the ARDS Network demonstrated significant mortality benefit, (22% reduction) with pressure and volume limited LPV (6ml/kg vs 12 ml/kg PBW) <sup>1</sup>. LPV may improve outcomes through several mechanisms including: decreased stretch and sheer forces applied to the alveolar wall (volutrauma and barotrauma), less cyclic recruitment-derecruitment of atelectatic areas of lung (atelectrauma) and attenuation of systemic cytokine response (biotrauma) <sup>4</sup>. Unfortunately, mortality in severe ARDS remains high – upwards of 40% <sup>5</sup>. A consequence of low tidal volume ventilation is a reduced ability to clear CO<sub>2</sub> due to reduced minute ventilation. A subset of patients cannot tolerate LPV without significant PaCO<sub>2</sub> elevation. In these patients, a higher respiratory rate to increase minute ventilation and lower PaCO<sub>2</sub> or permissive hypercapnia to facilitate low tidal volume ventilation, are used. Although initially thought to be benign or even protective, it is becoming increasingly evident that elevated CO<sub>2</sub> levels have significant physiological effects that may in fact be deleterious. This review will outline both the physiological and clinical sequelae of permissive hypercapnia in ARDS.

## 2. Effects of hypercapnic acidosis in animal models

## 2.1 Cytokine Response

Normal CO<sub>2</sub> arterial tension is generally within the range of 35– 45 mmHg. Classification of hypercapnia is variably defined but will be referred to in this review as mild, moderate and severe according to ranges of 46-50 mmHg, 50-75 mmHg and greater than 75 mmHg, respectively<sup>6</sup>. At the molecular level, hypercapnic acidosis inhibits production of pro-inflammatory cytokines and has been shown to attenuate inflammation related to ventilator induced lung injury (VILI) by inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and interleukin 8 (IL-8)<sup>7,8</sup>. Hypercapnic acidosis reduces oxidative reactions in the endotoxin-injured rat lung model<sup>9</sup>. Hypercapnic acidosis has also been associated with less severe VILI in isolated perfused rabbit lungs ex vivo<sup>10</sup> and in vivo<sup>11</sup>. It has been suggested by several groups that therapeutic hypercapnia might provide benefit in ARDS<sup>12-14</sup> and while decreasing host oxidative injury via hypercapnic acidosis would be of benefit in many cases, it may be deleterious when the etiology of ARDS is pulmonary infection and free radicals generated may play a role in facilitating bacterial injury and death<sup>15</sup>.

At the cellular level, hypercapnia alone lowers release of IL-8 from lipopolysaccharide-stimulated neutrophils<sup>16</sup> while hypercapnic acidemia attenuates lung neutrophil recruitment and function. This leads to a reduced host inflammatory response, but at the cost of impaired immune-mediated bactericidal activity in the lung<sup>14</sup>. The latter is also supported by a study showing that mice with *Pseudomonas aeruginosa* pneumonia exposed to hypercapnia develop impaired neutrophil function and have higher mortality as compared to air-exposed counterparts<sup>17</sup>.



Additional studies using neutrophil-depletion and *E. coli* mediated lung injury have found hypercapnic acidosis to be beneficial for oxygenation and lung compliance; however, there is no change in either lung inflammation or histological damage between hypercapnia and normocapnia<sup>18</sup>. Hypercapnia alone significantly enhances inflammatory reactions mediated by nitric oxide and secondary nitrating species in fetal rat lung epithelial cells exposed to lipopolysaccharide and inflammatory cytokines<sup>19</sup>. The duration of hypercapnic acidosis may influence its effects as attenuation of both histologic and physiologic indices of disease severity is observed with hypercapnic acidosis of short duration (< 6 hours)<sup>20</sup> and in models of acute lung injury (ALI) related to systemic sepsis<sup>21</sup>. Conversely, models using pulmonary sepsis-mediated ALI demonstrate no difference in physiologic or histologic indices of lung injury with hypercapnic acidosis<sup>22</sup> or worsened histologic indices and higher pulmonary bacterial loads in the setting of prolonged hypercapnic acidosis (>48 hrs duration) without appropriate anti-microbial therapy<sup>23</sup>.

## *2.2 Inhibition of lung epithelial cell repair and function*

Hypercapnic acidemia impairs pulmonary epithelial wound healing through two mechanisms<sup>24,25</sup>. Firstly, it slows epithelial repair of stretch-induced cell membrane injury<sup>24</sup>. Secondly, it inhibits repair of ventilator-induced pulmonary epithelial cell injury likely via inhibition of the NF- $\kappa$ B pathway by reducing cell migration and altering matrix metalloproteinase activity<sup>25</sup>. Recent clinical work lends support to these findings as pleural hypercarbia correlates with persistent alveolar-pleural fistulae post-lung resection<sup>26</sup>. Finally, short-term hypercapnia, independent of pH has been shown to impair alveolar epithelial cell function resulting in decreased alveolar fluid resorption<sup>27</sup>.

### 2.3 Renal effects

Acute hypercapnic acidosis has been shown to have several direct effects on renal vasculature in vivo. In conscious dogs, it reduces renal plasma flow<sup>28-30</sup>, increases renal vascular resistance<sup>30</sup>, stimulates robust activation of the renin-angiotensin-aldosterone system<sup>30,31</sup>, contributes to non-osmotic release of vasopressin<sup>29</sup> and diminishes renal free water excretion<sup>29</sup>. Ischemia-induced apoptosis of rat renal tubular cells in vitro is observed when hypercapnia and hypoxemia are simultaneously present<sup>32</sup>. In humans, hypoxemia and severe hypercapnia have been associated with reduced renal function<sup>33</sup>, whereas higher plasma norepinephrine levels are correlated with hypercapnia<sup>34</sup>. There is also a potential association with increased requirement for hemodialysis in patients using volume and pressure limited ventilation with hypercapnia<sup>35</sup>.

### 2.4 Diaphragmatic and skeletal muscle effects

Hypercapnic acidosis has been shown to modulate rat diaphragm myogenic response via endothelium-mediated alterations to diaphragmatic arteriolar tone. Hypercapnic acidosis with CO<sub>2</sub> values < 80 mmHg elicits enhancement of myogenic tone. Conversely, hypercapnic acidosis with CO<sub>2</sub> of >80 mmHg inhibits myogenic tone through endothelium-dependent inhibitory mechanisms. CO<sub>2</sub> values around 100 mm Hg appear to inhibit myogenic tone by both endothelium-dependent inhibitory mechanisms and direct effects of CO<sub>2</sub> on arteriolar smooth muscle tone<sup>36</sup>. In addition, skeletal muscle atrophy is associated with elevated CO<sub>2</sub> both in vitro and in vivo<sup>37</sup>. This may have relevance to the subset of ARDS patients with underlying chronic pulmonary disease in which muscle atrophy correlates with worse clinical outcomes.

### 2.5 Pulmonary circulation

Hypercapnic acidosis enhances pulmonary vasoconstriction in animals<sup>38,39</sup>. In particular, it correlates with significant elevation in mean pulmonary arterial pressures (mPAP), and pulmonary vascular resistance (PVR) in non-ARDS<sup>39</sup> and ARDS porcine models<sup>38</sup>, respectively.

### 2.6 Buffered hypercapnic acidosis

Pre-clinical studies have investigated whether hypercapnia or the associated respiratory acidemia exerts the physiological effects in models of ALI. Data from a rodent model using *E.coli* or endotoxin induced lung injury exhibited worse lung injury, and reduced wound healing in renal-buffered hypercapnic acidosis in comparison to normocapnic controls following 6 hours of lung protective ventilation<sup>40</sup>. Similarly, sepsis-induced ALI in rodents demonstrated similar degrees of physiologic and histologic injury in both bicarbonate-buffered hypercapnic acidosis and non-buffered normocapnic controls<sup>41</sup>.

While evidence from pre-clinical animal studies provides little to support the notion that hypercapnic acidosis is directly beneficial in ALI, it does highlight the need for further studies. In addition, a strategy using prolonged hypercapnia with untreated pulmonary infection demonstrates evidence of harm without appropriate antimicrobial therapy<sup>23</sup>.

## 3. Clinical studies of permissive hypercapnia with ARDS

### 3.1 Cardio-pulmonary effects of hypercapnia

Hypercapnia induces physiological changes in pulmonary and systemic circulation (figure 1). In healthy subjects, hypercapnic acidosis induces a rightward shift of the oxygen-hemoglobin dissociation curve <sup>42</sup> and lowers systemic vascular resistance (SVR) <sup>43</sup>. In post cardiopulmonary bypass surgery patients, hypercapnia results in globally reduced myocardial contractility; however, sympathetically driven tachycardia serves to maintain cardiac output when compensatory reserve exists <sup>44</sup>. Right ventricular function is particularly affected in the setting of post-operative hypercapnia such that there is increased right ventricular end-diastolic volume, decreased right ventricular ejection fraction (RVEF), and a significant increase in right ventricular stroke work index (RVSWI). These observations are in part due to increased pulmonary vascular resistance (PVR) owing to the direct vasoconstrictive effects of hypercapnic acidosis on pulmonary vasculature and to the accompanying rise in mPAP <sup>45-47</sup>. In non-ARDS patients with chronic pulmonary disease, Enson *et al.* demonstrated that respiratory acidosis but not hypercapnia alone causes elevation in PVR and mPAP <sup>48</sup>. In addition, their study showed that increases in mPAP may be more sensitive to hypoxia at lower pH values. Uncertainty remains as to the relative contribution of hypercapnia and respiratory acidosis to increases in PVR and mPAP in patients with ARDS.

Additional insight into alteration of pulmonary hemodynamics in ARDS can be obtained by studies examining coupling between the RV and pulmonary arterial circulation. The pulmonary vasculature is characterized by the arterial elastance of the pulmonary artery system synonymous with RV afterload ( $E_a$ ) whereas the RV system is characterized by the RV elastance ( $E_{es}$ ) <sup>49</sup>.  $E_{es}:E_a$  is the ratio of RV to pulmonary

artery (PA) elastance and reflects the mechano-energetic aspects of RV/PA coupling which determines RV stroke volume. When  $E_{es}:E_a$  is greater than 1 (normal range 1.5 to 2), the system is coupled providing adequate RV cardiac output at minimal energy cost<sup>50</sup>. In the context of hypercapnia, pulmonary vasoconstriction and elevated RV afterload may lead to an increase in  $E_a$ , uncoupling of the RV/PA system and subsequent RV dysfunction<sup>50</sup>.

### 3.2 Cardio-pulmonary effects of mechanical ventilation in ARDS

Studies of mechanical ventilation in patients with ARDS some 40 years ago first identified pulmonary capillary lesions leading to pulmonary hypertension, marked RV dysfunction with elevation of right ventricular stroke-work index and upwards of threefold increase in PVR<sup>51-54</sup>. Acute cor pulmonale represents the most severe form of RV dysfunction and has been the subject of numerous investigations in the ARDS patient population. It is variably defined using right heart catheterization, pulmonary artery catheterization and echocardiography.

Prior to the advent of LPV, acute cor pulmonale (defined as septal dyskinesia associated with a right ventricular to left ventricular end diastolic area ratio [RVEDA/LVEDA] greater than 0.6) was very common and could be observed in more than half of patients examined<sup>55</sup>. Not surprisingly, it is positively correlated with increases in plateau pressure (Pplat) during mechanical ventilation<sup>56</sup>. In a large pooled analysis using echocardiographic studies of patients with ARDS, the presence of acute cor pulmonale was 13%, 32% and 56% when Pplat values ranged between 18-26 cmH<sub>2</sub>O, 27-35 cmH<sub>2</sub>O and > 35 cmH<sub>2</sub>O, respectively. The highest mortality was observed in the two groups with highest Pplat values and in which acute cor pulmonale

was most prevalent<sup>56</sup>. However, similar studies using lung protective ventilation have described significantly lower rates<sup>57</sup>. For example, Osman *et al.* noted that right ventricular failure (defined as the presence of: mPAP > 25mmHg, central venous pressure (CVP) > pulmonary artery occlusion pressure (Ppao) and stroke volume index < 30ml/m<sup>2</sup>) was present in approximately 10% of ARDS patients<sup>58</sup>, whereas Boissier *et al* and Lheritier *et al* noted prevalence of acute cor pulmonale of 22%<sup>59</sup> and 22.5%, respectively<sup>60</sup>. Driving pressure (defined as the difference between Pplat and total PEEP) is a surrogate of lung stress that has been associated with survival and risk of cor pulmonale in ARDS patients which may suggest that a 'low pressure' ventilatory strategy could be RV-protective<sup>61</sup>. Lower overall rates of acute cor pulmonale in more recent studies likely relates to a combination of RV-protective ventilation strategies, heterogeneity in the definition itself, and to therapeutic ventilator adjustments based on its earlier recognition.

### 3.3 Cardiopulmonary effects of permissive hypercapnia in ARDS

In spite of these improvements, RV dysfunction remains prevalent and is linked to worsened outcomes in ARDS. For example, severe RV dysfunction is shown to be more prevalent in non-survivors of ARDS<sup>62</sup>. RV dysfunction in early ARDS as defined by a higher ratio of right atrial pressure to pulmonary artery occlusive pressure ( $P_{RA}/P_{pao}$ ) was independently associated with higher mortality<sup>63</sup>. The higher mortality exhibited in this study may in part be explained by the effects of mechanical ventilation in the era prior to adoption of LPV; however, studies of ARDS patients in the era following adoption of LPV also show a correlation between RV dysfunction and mortality. Boissier *et al* found significantly higher 28-day mortality in ARDS patients with severe RV dysfunction<sup>59</sup> and Osman *et al* found that elevated mPAP or CVP > Ppao respectively, to be

independently associated with 90-day mortality<sup>58</sup>. In addition, secondary analysis of ARDS patients from the Fluid and Catheter Treatment Trial (FACTT) demonstrated that elevation of transpulmonary gradient (mPAP - Ppao) or elevated pulmonary vascular resistance index, conferred a higher risk for 60-day mortality<sup>64</sup>.

Notwithstanding LPV, permissive hypercapnia coupled with moderate to severe ARDS may exert a synergistic effect that can lead to acute cor pulmonale. Widespread use of modern 2D echocardiography has not only improved our understanding of the effects of mechanical ventilation on RV function but has facilitated a better understanding of the relationship between mechanical ventilation, permissive hypercapnia and the development of acute cor pulmonale (table 1). Mekontso-Dessap *et al* utilized transesophageal echocardiography (TEE) in patients with severe ARDS to demonstrate that induction of hypercapnic acidosis with low tidal volume ventilation and increasing PEEP at constant plateau pressure, directly impaired RV function independent of the effects of PEEP<sup>65</sup>. Vieillard-Baron *et al* performed multivariate analysis of 75 patients with ARDS studied using transesophageal echocardiography (TEE). They found that elevated PaCO<sub>2</sub> was the sole individual predictor of acute cor pulmonale<sup>57</sup>. While the latter had no influence on mortality, the authors correctly identified acute cor pulmonale early in the study and introduced prone ventilation on day 3 in those patients that had PaO<sub>2</sub>/FiO<sub>2</sub> < 100 mmHg. Such adaptations may have mitigated the mortality associated with acute cor pulmonale<sup>66</sup>. Lheritier *et al* utilized a combination of TTE and TEE to study 200 patients with moderate to severe ARDS < 48 hrs from admission. Elevated PaCO<sub>2</sub> was significantly associated with acute cor pulmonale and PaCO<sub>2</sub> ≥ 60 mmHg was the only independent factor associated with acute cor pulmonale<sup>60</sup>. The study also found that the systolic pressure gradient between the right ventricle and right atrium ( $\Delta P_{max}$ ), an indirect measurement of

pulmonary vascular tone, correlated with  $\text{PaCO}_2$  and was significantly higher in those patients with  $\text{PaCO}_2 \geq 60$  mmHg<sup>60</sup>. Despite the study findings, there was no association between acute cor pulmonale at < 48 hrs from admission and 28-day mortality<sup>60</sup>. In a recent large prospective observational study (n=752) Mekontso-Dessap *et al* identified hypercapnia ( $\text{PaCO}_2 \geq 48$  mmHg) as a respiratory variable with statistically significant correlation with cor pulmonale (assessed by TEE) in ARDS patients receiving LPV. Acute cor pulmonale was found in 22% of the cohort and severe acute cor pulmonale (defined as  $\text{RV}:\text{LV} > 1$ ) was found in 7.2 % of patients and was an independent predictor of mortality<sup>67</sup>.

Secondary analysis of the ARDS Network Study published by Kregenow and colleagues found that the presence of hypercapnic acidosis at randomization to be associated with lower 28-day mortality in the group randomized to tidal volume of 12ml/kg (but no mortality difference in patients randomized to 6 ml/kg)<sup>68</sup> (table 2). This study had several limitations including being a retrospective secondary analysis, defining hypercapnic acidosis based upon a day 1 blood gas rather than sustained hypercapnic acidosis over time, as well as having very few patients in the hypercapnic acidosis group. As this was a secondary analysis there was no causality proven, but only an association inferred.

In contrast to the Kregenow *et al* study, two recent studies looking at mechanically ventilated patients within the ICU have called into question the safety of hypercapnic acidosis. The first study was retrospective and included 252,812 patients admitted to ICU with respiratory failure requiring mechanical ventilation during the first 24hr of their ICU admission. It found that hypercapnic acidosis in the first 24 hours of ICU admission was associated with higher in-hospital mortality compared with



compensated hypercapnia or normocapnia<sup>69</sup> (table 2). Interestingly both patients with compensated hypercapnia, and hypercapnic acidosis had higher mortality rates. This effect was consistent across all types of ICU admissions. This study's strength were the large number of patients included and the longitudinal nature of the data collection (data over a 14 year period from 171 ICUs). This study classified patients based upon a day 1 ABG and did not account for adjunctive treatments such as bicarbonate infusions and extracorporeal life support (ECLS).

The second study was a secondary analysis of 1899 patients from three prospective non-interventional cohort studies on ARDS patients. It demonstrated that severe hypercapnia, as defined by a  $\text{PaCO}_2 \geq 50$  mmHg, was associated with higher ICU mortality in a population with moderate to severe ARDS<sup>70</sup> (table 2). The authors used propensity matching to conduct a sensitivity analysis to demonstrate that hypercapnia independent of acidosis was associated with increased mortality while both had independent additive effects at increasing mortality. This study included patients from 927 ICUs in 40 countries. The investigators used the worst ABG in the first 48 hours of mechanical ventilation to stratify patients. Some of the weaknesses of this study included a high number of patients being excluded due to missing ABG data (11.5%) and no data collection on the use of adjunctive therapies such as bicarbonate infusions and ECLS.

### 3.3 Hypercapnia and organ dysfunction

Not surprisingly, the harmful effects of severe hypercapnia extend beyond the cardiopulmonary system. In the study by Nin *et al*, hypercapnic acidosis was associated with higher ventilator-associated complication rates (such as barotrauma) and more

organ failures including renal and cardiovascular dysfunction<sup>70</sup>. Further studies will be required to externally validate and elucidate the pathophysiologic basis for these findings and whether they share similarities to those described in animal models.

#### **4. Strategies of LPV when severe hypercapnia is present**

##### *4.1 LPV, dead space and hypercapnia*

Hypercapnia in ARDS patients can be an unintended consequence of LPV but may also be the result of higher dead space associated with increasing disease severity. This is important to identify early in the disease process as higher dead space fraction in early ARDS is independently associated with higher mortality<sup>71</sup>. Strategies aimed at reducing alveolar dead space along with the severity of hypercapnia can be employed but carry risk. Firstly, adequate lung recruitment to facilitate ventilation in ARDS often necessitates finding optimal PEEP but care must be used to avoid alveolar overdistention which can negatively affect pulmonary hemodynamics and RV function<sup>67</sup>. Secondly, titrating PEEP and driving pressure to achieve a desired tidal volume and PaCO<sub>2</sub> threshold during LPV is a complex process. For instance, Amato *et al* demonstrated in observational post hoc analysis of nine randomized controlled trials of patients with ARDS, that decreases in tidal volume or increases in PEEP are beneficial only when associated with decreased driving pressure<sup>61</sup>. Lastly, higher respiratory rates to correct hypercapnia are not tolerated in some patients with ARDS due to the development of dynamic hyperinflation and significant RV dysfunction<sup>72</sup>. In summary, strategies to lower PaCO<sub>2</sub> can be associated with significant harm and their use must be weighed against the risks associated with permissive hypercapnia.

#### 4.2 Prone Positioning

Placing patients with severe ARDS in prone position has been demonstrated to improve oxygenation, compliance and early institution improves mortality<sup>73</sup>. Some studies, however, have suggested that it is the decrease in PaCO<sub>2</sub> associated with a reduction in alveolar dead space rather than increased PaO<sub>2</sub> that might best reflect the degree of functional lung recruited with prone positioning<sup>74,75</sup>. Unfortunately, the only prospective randomized controlled trial to demonstrate mortality benefit with prone positioning (PROSEVA) did not directly evaluate alveolar recruitment with prone positioning<sup>73</sup>. In addition, a retrospective analysis of PROSEVA by Albert et al, demonstrated that increased survival with proning was not predicted by improvement in gas exchange as determined by blood gas analysis.<sup>76</sup> Nonetheless, prone positioning can lower PaCO<sub>2</sub> and unload the RV in selected groups of ICU patients and is an important tool to improve patient outcomes in severe ARDS.<sup>77</sup>

#### 4.3 Extracorporeal veno-venous CO<sub>2</sub> removal (ECCO<sub>2</sub>R)

Debate continues over the role of extracorporeal devices in the management of ARDS. Specifically, there has been renewed interest in extracorporeal veno-venous CO<sub>2</sub> removal (ECCO<sub>2</sub>R) which offers efficient CO<sub>2</sub> removal with relatively low blood flow rates. A recent experimental porcine model by Morimont *et al* sought to determine whether using ECCO<sub>2</sub>R during LPV could improve pulmonary hemodynamics and RV function in early ARDS<sup>38</sup>. Institution of ECCO<sub>2</sub>R effectively corrected acidosis and hypercapnia during LPV. In addition, PVR and mPAP were significantly reduced and RV-pulmonary arterial (Ees:Ea) coupling was improved. Changes in both pH and PaCO<sub>2</sub> were highly correlated with changes in mPAP. Whether findings from this study are

translatable into human patients with ARDS is unknown. At minimum, it provides rationale to initiate prospective studies in patients with moderate to severe ARDS using early institution of ECCO<sub>2</sub>R to normalize pH and CO<sub>2</sub> in conjunction with current standards of LPV.

#### *4.4 Ultralow tidal volume ventilation and maintenance of normocapnia*

Several recent trials have examined ultra-low tidal volume ventilation (3-4 ml/kg) in combination with ECCO<sub>2</sub>R to determine its feasibility and whether additional benefit beyond current lung protective ventilation exists<sup>78-80</sup>. In theory, ultra-low tidal volume ventilation lowers the risk of alveolar over-distension that can still occur despite our current use of LPV<sup>81</sup>. It prevents the hemodynamic changes (acute cor pulmonale and/or RV failure) and it facilitates a 'least damaging' ventilatory approach (substantially lower P<sub>plat</sub> and driving pressure values) that some have speculated would confer survival benefit<sup>82</sup>. While the study by Bein *et al* did not show an overall difference in 28 or 60-day ventilator free days between groups, a post-hoc analysis demonstrated that patients with severe hypoxemia at randomization (PaO<sub>2</sub>/FiO<sub>2</sub> < 150 mmHg) had a significantly shorter ventilation period as assessed by higher 60-day ventilator free days<sup>78</sup>. Additional studies on this front are underway (SUPERNOVA and REST). Yet despite these trials, it remains unclear whether the 'least damaging' ventilation approach with ultralow tidal volume ventilation and maintenance of normocapnia should be applied to patients with moderate ARDS or severe ARDS and whether it confers benefit over current standards of LPV with maintenance of normocapnia in either of these respective groups.

#### *4.5 The role of buffers in management of ARDS*

There is substantial uncertainty over the role of buffers in the management of respiratory acidosis associated with LPV. While the ARMA trial permitted sodium bicarbonate infusions in the low tidal volume protocol when pH fell below 7.15<sup>1</sup>, their use warrants caution. A reasonable approach would be to utilize a strategy similar to the protocol used in the low tidal volume ventilation group of the ARMA trial<sup>1</sup>.

## 5. Summary

Pre-clinical studies of ARDS have provided insight into the physiologic effects of hypercapnic acidosis; however, the relative contribution of hypercapnia on mortality in animal models remains uncertain except in the context of active untreated pulmonary infection where it is associated with worsened outcomes.

Clinical studies in patients with ARDS have shown an association between severe hypercapnia, acute cor pulmonale and mortality. Severe hypercapnia has also been associated with higher rates of non-cardiovascular organ dysfunction and ICU mortality in patients with moderate to severe ARDS.

Ultra lung protective ventilation with maintenance of normocapnia using extracorporeal CO<sub>2</sub> removal offers potential advantages over current standards of lung protective ventilation. It remains uncertain, however, whether this strategy should be applied to patients with moderate ARDS, severe ARDS, or both. Furthermore, it remains to be determined whether this strategy offers additional benefit in either of these patient groups as compared to LPV with maintenance of normocapnia.

## 6. Final Thoughts

Severe hypercapnia has deleterious consequences in patients with moderate to severe 'Berlin Criteria' ARDS. For clinicians managing such patients, we suggest controlling severe hypercapnia such that  $\text{PaCO}_2$  be kept below 50mmHg in line with current evidence<sup>83</sup>. In addition to examining ultra low tidal volume ventilation with ECCO<sub>2</sub>R, it is time to reassess current LPV strategies in patients with moderate to severe ARDS. A larger, adequately powered randomized study using LPV comparing maintenance of normocapnia with ECCO<sub>2</sub>R versus permissive hypercapnia is warranted.

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## Tables

Citation	Study Design	Results	Comments
Vieillard-Baron et al <sup>57</sup> (2001)	Prospective single center, open design n = 75	Multivariate regression analysis: PaCO <sub>2</sub> independently associated with ACP. OR 1.15, 95% CI 1.05– 1.25, p < .0001  Mortality not influenced by presence of ACP	ACP defined as ratio of RVEDA/LVEDA > 0.6 by TEE  MV: Pplat limited to ≤ 30 cm H <sub>2</sub> O, tidal volume of 6–9 mL/kg (PBW), PEEP range 3–15 cm H <sub>2</sub> O
Lheritier et al <sup>60</sup> (2013)	Prospective multi-center n = 200	Multivariate regression analysis: PaCO <sub>2</sub> > 60 mmHg strongly associated with ACP. OR 3.70, 95% CI 1.32–10.38, p = 0.01  ACP not independently associated with mortality	ACP defined as ratio RVEDA/LVEDA > 0.6 by TEE  MV: Pplat ≤ 30 cm H <sub>2</sub> O, tidal volume and PEEP according to expert recommendations from the Societe de Reanimation de Langue Francaise
Mekontso-Dessap et al <sup>67</sup> (2016)	Prospective multi-center n = 752	Multivariate regression analysis: Severe ACP independently associated with in hospital mortality. OR 2.00, 95% CI 1.03– 3.88, p = 0.04  PaCO <sub>2</sub> > 48 mmHg associated with ACP. OR 2.39, CI 1.62–3.52, p < 0.01	ACP and severe ACP defined as ratio of RVEDA/LVEDA > 0.6 and > 1.0 respectively with presence of septal dyskinesia by TEE  MV: Pplat ≤ 30 cm H <sub>2</sub> O, tidal volume of 6–8 mL/kg (PBW), PEEP 8 ± 4 cm H <sub>2</sub> O

**Table 1 - Summary of clinical studies showing correlation between hypercapnia, severe RV dysfunction/acute cor pulmonale and mortality in mechanically ventilated patients with ARDS.** ACP = Acute cor pulmonale, CI = Confidence interval, MV = Mechanical ventilation, OR = Odds ratio, PaCO<sub>2</sub> = Partial pressure of arterial carbon dioxide, Pplat = plateau pressure, PEEP = Positive end expiratory pressure, PBW = Predicted body weight, RVEDA/LVEDA = Ratio of right ventricular end diastolic area to left ventricular end diastolic area, TEE = Trans esophageal echocardiography

Citation	Study Design	Results	Comments
Kregenow et al <sup>68</sup> (2006)	Retrospective secondary analysis of ARMA trial (ARDS Network) multi-center RCT (2000) n = 861	Multivariate regression analysis:  Lower 28 day mortality associated with hypercapnic acidosis in 12 ml/kg (PBW). Adjusted odds ratio 0.14, 95% CI 0.03–0.70, p = .016  No reduction in 28 day mortality associated with hypercapnic acidosis in low tidal volume ventilation group (6ml/kg PBW)	HA based on day 1 ABG measurement only. Too few patients with sustained HA to analyze  Significant number of patients missing day 1 ABG  No data collected on intravenous bicarbonate infusion usage
Tiruvoipati et al <sup>69</sup> (2017)	Retrospective multi-center international study n = 252,812	Multivariate regression analysis:  Higher hospital mortality for patients with hypercapnic acidosis, and compensated hypercapnia, adjusted (for severity of illness) OR 1.74, 95% CI, 1.62–1.88 and 1.18; 95% CI, 1.10–1.26 respectively, as compared to normocapnia with normal pH, p < 0.001	Strength of this study was the high number of patients included  Used only day 1 ABG data to classify  No data collected on use of intravenous bicarbonate infusion or extracorporeal life support
Nin et al <sup>70</sup> (2017)	Secondary analysis of three prospective non-interventional cohort studies (multi-center international) n = 1899	Multivariate regression analysis: Significantly higher ICU mortality in patients with maximum PaCO <sub>2</sub> of ≥ 50 mmHg (severe hypercapnia) during the first 48 h of MV, OR 1.93, 95% CI 1.32–2.81, p = 0.001  Additional binomial logistic model omitting acidosis: PaCO <sub>2</sub> of ≥ 50 mmHg independently associated with a higher risk of ICU mortality, OR 2.40, 95% CI 1.67–3.46, p < 0.001  Higher rates of organ failure and complications with PaCO <sub>2</sub> of ≥ 50 vs < 50 mmHg: Cardiovascular failure (p = .001), renal failure (p = 0.013), barotrauma (p = .001)	Strength is a secondary analysis of multinational, multicenter cohort from ICUs in 40 countries  Used worst PaCO <sub>2</sub> from ABGs within 48 hours of initiation of MV  11.5% of patients excluded due to missing ABG data  No data collected on use of intravenous bicarbonate infusion or extracorporeal life support

**Table 2: Summary of clinical studies showing effects of hypercapnia and hypercapnic acidosis on mortality in mechanically ventilated patients with ARDS.** ABG = arterial blood gas, CI = Confidence interval, HA = Hypercapnic acidosis, MV = Mechanical ventilation, OR = Odds ratio, PaCO<sub>2</sub> = Partial pressure of arterial carbon dioxide, PBW = predicted body weight



**Figure Legends**

**Figure 1** - Systemic effects of hypercapnia. HR = heart rate, mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance, RVEF = right ventricular ejection fraction, RVSWI = right ventricular stroke work index, SVR = systemic vascular resistance

